

WHAT IS CLAIMED IS:

1. A substantially pure conotoxin peptide having the general formula I:

Xaa-Xaa₀-Xaa₁-Cys-Cys-Gly-Xaa₂-Xaa₃-Xaa₄-Cys-Xaa₅-Xaa₆-Cys-Xaa₇ (SEQ ID NO:1)
 wherein Xaa is *des*-Xaa, Asn, Gln or pyro-Glu; Xaa₀ is *des*-Xaa₀, Gly, Ala, Glu, γ-carboxy-Glu (Gla) Asp, Asn, Ser, Thr, g-Asn (where g is glycosylation), g-Ser or g-Thr; Xaa₁ is Val, Ala, Gly, Leu, Ile, Ser, Thr, g-Asn, g-Ser or g-Thr; Xaa₂ is Phe, Tyr, meta-Tyr, ortho-Tyr, nor-Tyr, mono-halo-Tyr, di-halo-Tyr, O-sulpho-Tyr, O-phospho-Tyr, nitro-Tyr, Trp (D or L), neo-Trp, halo-Trp (D or L), any synthetic aromatic amino acid, an aliphatic amino acid bearing linear or branched saturated hydrocarbon chains such as Leu (D or L), Ile and Val or non-natural derivatives of the aliphatic amino acid; Xaa₃ is Lys, Arg, homolysine, homoarginine, ornithine, nor-Lys, His, N-methyl-Lys, N,N'-dimethyl-Lys, N,N',N''-trimethyl-Lys, any synthetic basic amino acid, Ser, Thr, g-Ser, g-Thr or any hydroxylated synthetic residue; Xaa₄ is an aliphatic amino acids bearing linear or branched saturated hydrocarbon chains such as Leu (D or L), Ile and Val or non-natural derivatives of the aliphatic amino acid, Met, Phe, Tyr, meta-Tyr, ortho-Tyr, nor-Tyr, mono-halo-Tyr, di-halo-Tyr, O-sulpho-Tyr, O-phospho-Tyr, nitro-Tyr, Trp (D or L), neo-Trp, halo-Trp (D or L) or any synthetic aromatic amino acid; Xaa₅ is His, Ser, Thr, g-Ser, g-Thr, an aliphatic amino acid bearing linear or branched saturated hydrocarbon chains such as Leu (D or L), Ile and Val, non-natural derivatives of the aliphatic amino acid, Phe, Tyr, meta-Tyr, ortho-Tyr, nor-Tyr, mono-halo-Tyr, di-halo-Tyr, O-sulpho-Tyr, O-phospho-Tyr, nitro-Tyr, Trp (D or L), neo-Trp, halo-Trp (D or L) or a synthetic aromatic amino acid; Xaa₆ is Pro, hydroxy-Pro (Hyp) or g-Hyp; Xaa₇ is *des*-Xaa₇, Gly, Ala, Lys, Arg, homolysine, homoarginine, ornithine, nor-Lys, His, N-methyl-Lys, N,N'-dimethyl-Lys, N,N',N''-trimethyl-Lys or any synthetic basic amino acid; and the C-terminus contains a free carboxyl group or an amide group.

2. The substantially pure conotoxin peptide of claim 1 selected from the group consisting of:

Asn-Gly-Val-Cys-Cys-Gly-Xaa₁-Xaa₂-Leu-Cys-His-Xaa₃-Cys (SEQ ID NO:2);

Gly-Val-Cys-Cys-Gly-Xaa₁-Xaa₂-Leu-Cys-His-Xaa₃-Cys (SEQ ID NO:3);

Gly-Ile-Cys-Cys-Gly-Val-Ser-Phe-Cys-Xaa₁-Xaa₃-Cys (SEQ ID NO:4);

Ala-Cys-Cys-Gly-Xaa₁-Xaa₂-Leu-Cys-Ser-Xaa₃-Cys (SEQ ID NO:5);

Xaa₄-Thr-Cys-Cys-Gly-Xaa₁-Arg-Met-Cys-Val-Xaa₃-Cys-Gly (SEQ ID NO:6); and

Ser-Thr-Cys-Cys-Gly-Phe-Xaa₂-Met-Cys-Ile-Xaa₃-Cys-Arg (SEQ ID NO:7), wherein Xaa₁ is Tyr, mono-halo-Tyr, di-halo-Tyr, O-sulpho-Tyr, O-phospho-Tyr, nitro-Tyr; Xaa₂ is Lys, N-methy-Lys, N,N-dimethyl-Lys or N,N,N-trimethyl-Lys; Xaa₃ is Pro or hydroxy-Pro, preferably hydroxy-Pro; Xaa₄ is Gln or pyro-Glu; and the C-terminus contains a carboxyl or amide group.

3. The substantially pure conotoxin peptide of claim 2, wherein Xaa₁ is Tyr.
4. The substantially pure conotoxin peptide of claim 2, wherein Xaa₂ is Lys.
5. The substantially pure conotoxin peptide of claim 2, wherein Xaa₃ is hydroxy-Pro.
6. The substantially pure conotoxin peptide of claim 2, wherein Xaa₄ is Gln.
7. The substantially pure conotoxin peptide of claim 2, wherein Xaa₁ is Tyr, Xaa₂ is Lys, Xaa₃ is hydroxy-Pro and Xaa₄ is Gln.
8. The substantially pure conotoxin peptide of claim 2, wherein halo is iodine.
9. The substantially pure conotoxin peptide of claim 8, wherein Xaa₃ is mono-iodo-Tyr.
10. The substantially pure conotoxin peptide of claim 8, wherein Xaa₃ is di-iodo-Tyr.
11. A substantially pure conotoxin peptide derivative comprising a derivative of the conotoxin peptide of claim 2.
12. The substantially pure conotoxin peptide derivative of claim 11, wherein the Arg residues may be substituted by Lys, ornithine, homoargine, nor-Lys, N-methyl-Lys, N,N-dimethyl-Lys, N,N,N-trimethyl-Lys or any synthetic basic amino acid; the Xaa₂ residues may be substituted by Arg, ornithine, homoargine, nor-Lys, or any synthetic basic amino acid; the Tyr residues may be substituted with any synthetic aromatic containing amino acid; the Ser residues may be substituted with Thr or any synthetic hydroxy containing amino acid; the

Thr residues may be substituted with Ser or any synthetic hydroxy containing amino acid; the Phe and Trp residues may be substituted with any synthetic aromatic amino acid; the Asn, Ser, Thr or Hyp residues may be glycosylated; the Cys residues may be in D or L configuration; the Cys residues may be substituted with homocysteine (D or L); the Tyr residues may also be substituted with the 3-hydroxyl or 2-hydroxyl isomers (meta-Tyr or ortho-Tyr, respectively) and corresponding O-sulpho- and O-phospho-derivatives; the acidic amino acid residues may be substituted with any synthetic acidic amino acid, e.g., tetrazolyl derivatives of Gly and Ala; pairs of Cys residues may be replaced pairwise with isoteric lactam or ester-thioether replacements, such as Ser/(Glu or Asp), Lys/(Glu or Asp) or Cys/Ala combinations; and the aliphatic amino acids may be substituted by synthetic derivatives bearing non-natural aliphatic branched or linear side chains C_nH_{2n+2} up to and including $n=8$.

13. The substantially pure conotoxin peptide of claim 2, wherein said peptide has the sequence set forth in SEQ ID NO:2, wherein Xaa₁ is Tyr, Xaa₂ is Lys and Xaa₃ is hydroxy-Pro.
14. The substantially pure conotoxin peptide of claim 2, wherein said peptide has the sequence set forth in SEQ ID NO:3, wherein Xaa₁ is Tyr, Xaa₂ is Lys and Xaa₃ is hydroxy-Pro.
15. The substantially pure conotoxin peptide of claim 2, wherein said peptide has the sequence set forth in SEQ ID NO:4, wherein Xaa₁ is Tyr and Xaa₃ is hydroxy-Pro.
16. The substantially pure conotoxin peptide of claim 2, wherein said peptide has the sequence set forth in SEQ ID NO:5, wherein Xaa₁ is Tyr, Xaa₂ is Lys and Xaa₃ is hydroxy-Pro.
17. The substantially pure conotoxin peptide of claim 2, wherein said peptide has the sequence set forth in SEQ ID NO:6, wherein Xaa₁ is Tyr, Xaa₃ is hydroxy-Pro and Xaa₄ is Gln.
18. The substantially pure conotoxin peptide of claim 2, wherein said peptide has the sequence set forth in SEQ ID NO:7, wherein Xaa₂ is Lys and Xaa₃ is hydroxy-Pro.

19. A method for inducing analgesia in a mammal which comprises administering a therapeutically effective amount of a conotoxin peptide of claim 1.
20. The method of claim 19, wherein said administration comprises using a delivery means selected from the group consisting of a pump, microencapsulation, a continuous release polymer implant, macroencapsulation, naked or unencapsulated cell grafts, injection and oral administration.
21. The method of claim 20, wherein administration is intrathecal injection.
22. The method of claim 20, wherein administration is intracerebroventricular injection.
23. The method of claim 20, wherein administration is by pump.
24. The method of claim 20, wherein the amount of conotoxin peptided administered is between about 0.001 mg/kg to about 250 mg/kg.
25. The pharmaceutical composition comprising a therapeutically effective amount of the conotoxin peptide of claim 1 or a pharmaceutically acceptable salt or solvate thereof and a pharmaceutically acceptable carrier.
26. The composition of claim 25 which further comprises one or more drugs useful in the treatment of pain.
27. An isolated nucleic acid comprising a nucleotide sequence coding for contotoxin propeptide selected from the group consisting of:
- (a) the amino acid sequence set forth in SEQ ID NO:12;
 - (b) the amino acid sequence set forth in SEQ ID NO:14;
 - (c) the amino acid sequence set forth in SEQ ID NO:16; and
 - (d) the amino acid sequence set forth in SEQ ID NO:18.

28. The isolated nucleic acid of claim 27 comprising a nucleotide sequence selected from the group consisting of:

- (a) the nucleotide sequence set forth in SEQ ID NO:11;
- (b) the nucleotide sequence set forth in SEQ ID NO:13;
- (c) the nucleotide sequence set forth in SEQ ID NO:15; and
- (d) the nucleotide sequence set forth in SEQ ID NO:17.

29. An isolated conotoxin propeptide selected from the group consisting of:

- (a) the amino acid sequence set forth in SEQ ID NO:12;
- (b) the amino acid sequence set forth in SEQ ID NO:14;
- (c) the amino acid sequence set forth in SEQ ID NO:16; and
- (d) the amino acid sequence set forth in SEQ ID NO:18.

30. A method of identifying compounds that mimic the analgesia activity of the peptide of claim 1, comprising the steps of:

- (a) conducting a biological assay on a test compound to determine the analgesia activity; and
- (b) comparing the results obtained from the biological assay of the test compound to the results obtained from the biological assay of the peptide of claim 1.

31. A method for identifying a desired activity encoded by a genomic DNA in a sample comprising the steps of:

- (a) providing a genomic DNA;
- (b) contacting the DNA with a nucleic acid probe which is substantially complementary to a predetermined sequence of a gene encoding for the peptide of claim 1; and
- (c) detecting whether the DNA of the sample formed a hybrid with the probe.